Annals of Internal Medicine | ACADEMIA AND CLINIC

The Practitioner's Dilemma: Can We Use a Patient's Race To Predict Genetics, Ancestry, and the Expected Outcomes of Treatment?

Donald A. Barr, MD, PhD

Recent research has identified genetic traits that can be used in a laboratory setting to distinguish among global population groups. In some genetic analyses, the population groups identified resemble groups that are historically categorized as "races." On the basis of these associations, some researchers have argued that a patient's race can be used to predict underlying genetic traits and from these traits, the expected outcomes of treatment. Others have questioned the use of race in this way, arguing that racially defined groups are so heterogeneous that predictions of individual characteristics derived from group averages are bound to be problematic.

Practitioners today face the dilemma of translating this scientific debate into clinical decisions made 1 patient at a time. Is it or is it not appropriate to use a patient's self-identified "race" to help decide treatment?

In contrast to the global population groups identified by genetic studies, the U.S. population has experienced substantial genetic admixture over time, weakening our ability to distinguish groups on the basis of meaningful genetic differences. Nonetheless, many researchers have suggested that these differences are still sufficient to identify racially specific uses for pharmaceutical and other treatments. A review of recent research on the treatment of hypertension and congestive heart failure finds that race-specific treatments of this type carry a substantial risk for treating patients—black or white—inappropriately, either by withholding a treatment that may be effective or by using a treatment that may be ineffective. Only by moving beyond historical concepts of "race" to examining a patient's individual socioeconomic, cultural, behavioral, and ancestral circumstances can a practitioner select the treatment that is most likely to be effective and in doing so, can best serve that patient's needs.

Ann Intern Med. 2005;143:809-815. www.annals.org
For author affiliation, see end of text.

The decoding of the human genome has opened the door to an exciting realm that may fundamentally alter the trajectory of many diseases. For many practitioners, however, recent advances in our understanding of genomics and the genetics of ancestry have left us with an unanswered question. In the clinical context, does a patient's race provide an adequate proxy for genetics?

The relationship between genomics and what we call "race" is complex and changes frequently. Understanding it requires familiarity with esoteric methods. A practitioner may find it difficult to know what to do when dealing with the problems of an individual patient. Is it or is it not appropriate to use that patient's ascribed or self-identified race to help decide treatment? Practitioners face this dilemma on a regular basis.

The debate over using race as a proxy for genetics and associated treatment outcomes is often heated. A recent op-ed piece in *The New York Times* opined that "[r]ace is merely a shorthand that enables us to speak sensibly, though with no great precision, about genetic rather than cultural or political differences" (1). Consistent with this approach, a physician recently described her approach to care (2):

> Almost every day at the Washington drug clinic where I work as a psychiatrist, race plays a useful diagnostic role. . . . [C]linical experience and pharmacologic research show that blacks metabolize antidepressants more slowly than Caucasians and Asians. . . . So I start all black patients with a lower dose, then take it from there.

On the other side of the aisle are scholars who state (3):

> A racial designation in the context of medical management not only defies everything we have learned from biology, genetics, and history but also opens the door to inequities in medical care. . . . Since "race" is biologically meaningless, how will a physician know whether a given patient (who may identify with 2 races) has the combination of alleles that will ensure the efficacy of the drug? And what effect will racial profiling in the choice of therapy have on the bond of trust between patients and physicians?

Whom should practitioners believe?

Recent Research in the Genetics of Race and Ancestry

Rosenberg and colleagues (4) published a seminal paper in 2002 that addressed the issue of race as a proxy for genetics. They analyzed the genetic structure of tissue samples taken from 1056 individuals drawn from 52 population groups around the globe. Each group represented a distinct geographic area, and the individuals within each group had remained relatively stable geographically over several generations. The authors asked whether the genetic differences among these population groups were distributed into recognized racial groups.

(There is an important caveat to consider here. Study-

See also:

Web-Only
Conversion of tables into slides

Table 1. **Geographic Origins of Groups Defined by Genetic Clustering on the Basis of the Predefined Number of Groups***

Predefined Groups, *n*	Geographic Origins of Genetic Groups
2	1. Sub-Saharan Africa, Europe, Middle East, Central Asia, South Asia 2. East Asia, Oceania, Americas
3	1. Sub-Saharan Africa 2. Europe, Middle East, Central Asia, South Asia 3. East Asia, Oceania, Americas
4	1. Sub-Saharan Africa 2. Europe, Middle East, Central Asia, South Asia 3. East Asia, Oceania 4. Americas
5	1. Sub-Saharan Africa 2. Europe, Middle East, Central Asia, South Asia 3. East Asia 4. Oceania 5. Americas
6	1. Sub-Saharan Africa 2. Europe, Middle East, Central Asia, South Asia 3. East Asia 4. Oceania 5. Americas 6. Kalash (a tribe of approximately 4000 people in northwestern Pakistan)

* Data from reference 4.

ing only geographically stable samples does not consider the effects of intermarriage and other forms of interbreeding—often called "genetic admixture." In populations such as the United States, in which extensive genetic admixture has occurred over centuries, sorting population groups reliably on the basis of genetic differences is difficult if not impossible. Rosenberg and colleagues' analysis of the genetic structure of ethnic populations of the Middle East, in which substantial admixture has occurred over time, confirms this.)

To appreciate how Rosenberg and colleagues' research was performed, imagine 2 groups of scientists in adjoining rooms separated by a locked door. One group is made up of geneticists, the other of social scientists. The geneticists are provided with a set of 1056 tissue samples with no labeling of their source, and they are asked to sort these samples into groups based on similarities in genetic structure. A computer has been programmed to compare slight differences in the molecular structure of 377 different DNA segments to sort these tissue samples into groups. These segments are called "microsatellites," and they represent parts of the DNA that have no known genetic function and are known from previous research to exhibit substantial variation in nucleotide structure across individuals. (The number of segments that optimizes the computer's ability to identify genetic differences among populations is thought to be 377.) The computer doesn't choose the number of groups into which the samples will be sorted; the scientists do. Once the number of groups is arbitrarily chosen by those scientists, the computer uses a statistical algorithm to define the best grouping.

Think of a deck of cards. Imagine that you are asked to use a computer to sort them into groups based on similarities and differences. When arbitrarily instructed to sort the cards into 2 groups, you will see the cards divided by color: black and red. If you instruct the computer to sort the cards into 3 groups, you might get a group consisting of face cards, another of numbered red cards, and another of numbered black cards. Changing to 4 groups will sort the cards into the suits you recognize in most card games.

Rosenberg and colleagues took a similar approach, asking a computer first to sort the tissue samples into 2 groups, then 3 groups, and so on up to 6 groups. The computer first determined that approximately 95% of the difference identified in DNA structure occurred within populations at the level of the individual tissue sample in ways that did not allow it to differentiate among population groups. Only 5% of the difference in structure occurred among groups. Nevertheless, solely on the basis of that 5% of the difference, the statistical algorithm used by the computer could separate the tissue samples into the various numbers of groups selected by the scientists.

We now return to our imaginary scientists in adjoining rooms. While the geneticists have been doing their work, the social scientists in the adjoining room have had a different task. They are told the geographic origin of each tissue sample, and they are asked to sort the samples first by continent of origin and then within continents by region.

After both groups of scientists have done their job, the door is unlocked, and the scientists are asked to compare their results. Does grouping the tissue samples by genetic structure recreate the grouping by geographic origin?

In Rosenberg and colleagues' study, the answer was "yes": "Genetic clusters often corresponded closely to predefined regional or population groups or to collections of geographically and linguistically similar populations" (4). May information on genetic ancestry be useful in clinical practice? Again, the answer was "yes": "Information about a patient's population of origin might provide healthcare practitioners with information about risk when direct causes of disease are unknown" (4).

Does this mean that we can use a patient's race as a proxy for ancestry and to predict genetic structure with accuracy? Although Rosenberg and colleagues did not address this question explicitly, the answer seems to be "no." To understand why, let us examine how the genetically defined groups look from a geographic perspective, varying the arbitrarily defined number of groups from 2 to 6. **Table 1** shows these results.

The Origins of Racial Categories

For more than 250 years, there have been 4 "races" in much of the Western world: white, black, Asian, and Native American. European explorers defined these categories as they set out to identify (and conquer) new continents, and Carl Linnaeus cataloged and described these categories

in the 1700s in successive editions of his work *Systema Naturae*. Linnaeus divided the human species into what he perceived as its 4 subspecies: *Afer niger* (African black), *Americanus rubescus* (American red), *Asiaticus luridus* (Asian yellow), and *Europaeus albus* (European white).

In reporting birth and death rates for 2002, the federal government's *National Vital Statistics Reports* continued to sort Americans into the same 4 groups described by Linnaeus in the 1700s. The U.S. Census Bureau has also preserved these racial categories largely intact. (There is a movement to separate out the indigenous peoples of the Pacific Islands—"Oceania" in the groupings of Rosenberg and colleagues' study—in both census data and the reporting of vital statistics.)

If we look only at the group of 4 origins in **Table 1**, the geneticists seem to have sorted the tissue samples into what we generally recognize as races—although some groups that are considered Asian by race have clustered with the Europeans. However, just as the deck of cards is sorted differently depending on the preselected number of groups, so does the world's population look different on the basis of that preselected number. Select "4," and we have the cards by suits and people by Linnaeus' races. Select "2," and we have cleaved both the deck and the globe approximately in half. Select "6," and the global population starts to get somewhat confusing. Which is the best number for sorting the human population? There cannot be an answer to this question without applying arbitrary measures to the concept of what is "best."

The genetics of human populations may start with broad continental groupings that bear a rough resemblance to Linnaeus' racial categories, but knowledge of individual ancestry provides much more detailed and relevant information. Consider my ancestors and those of my wife. Mine came on the *Mayflower* to the Plymouth Colony, and hers fled the 19th-century pogroms aimed at Russian Jews. Both were from Europe. We both check the "white" box on all the official forms. To learn about our health risks based on our ancestry, you will need to know that I am a mixture of Anglo-Saxon and Celt, while my wife is an Ashkenazi Jew. From our race (white), you can only guess our genetic traits. From knowing the specifics of our ancestry, you can make reasoned projections of our health risks.

Let us shift our analysis from my family to that of a classic, although tragic, figure from Western literature. Othello, as Shakespeare described him, had a record as a successful general. When the Duke of Venice needed someone to lead his forces against the invading Turks, he chose Othello. Desdemona, the daughter of Barbantio, one of the leading citizens of Venice, also chose Othello—as a husband. The problem is that Othello is not Venetian—he is a dark-skinned Moor. On learning that his daughter has chosen to be with Othello, Barbantio accosts Othello (act 1, scene 2): O thou foul thief, where hast thou stow'd my daughter? / Damn'd as thou art, thou hast enchanted her / . . . to [thy] sooty bosom.

Othello's problem is that his "sooty bosom" (that is, his dark skin) has cast him as an outsider of a different race. Moors were from northwestern Africa, what we now recognize as Algeria and Morocco. In Shakespeare's time, most Europeans considered Moors to be black. This racial categorization of Moors persisted well into the 20th century (5). However, the genetic clustering identified by Rosenberg and colleagues suggests that North Africans and those from the Middle East are genetically more similar to Europeans than they are to sub-Saharan Africans (4). Consistent with this genetic grouping, the U.S. Census Bureau categorizes Moroccans and other North Africans as white (6). By today's standards, Desdemona's husband was white.

The problem arises from using the 4 historical categories of race to sort people. Even for populations that have experienced relatively little admixture, race and genetics overlap only partially and imperfectly. For example, Pakistanis, Indians, and other South Asians are Asian by race but are genetically more similar to Europeans than to East Asians (4).

A practitioner without a complete understanding of these issues might sort Mr. Othello, a dark-skinned Moroccan patient with hypertension, into the "black race" category and his Venetian neighbor Mr. Barbantio into the "white race" category. However well-intentioned this use of race as a predictor of genetic structure might be, it would be flawed in this case. Categorizing an Ethiopian or Somali patient as black is also a mistake. Genetically, these populations are midway between Africans and Europeans, and they tend to resemble Europeans more so than they do sub-Saharan Africans (7, 8). The cases of the Moor and the Ethiopian patients illustrate the point that historical and contemporary concepts of race are often inadequate proxies for genetics.

As complex as the issue of race and genetics is for North Africans and other transitional populations, the issue is even more complex with a population in which extensive genetic admixture has occurred, such as the United States. Most African Americans, for example, have mixed ancestry, involving African, European, and Native American genetic traits at varying levels (9). A person who self-identifies as African American may be as genetically similar to a European as to a sub-Saharan African. Genetic variation within the African-American population is substantial (10), and failure to take this variation into account risks identifying spurious associations between race and genetic traits (11).

Race and Cardiovascular Disease

Tang and colleagues (12) used the same genetic sorting method used by Rosenberg and colleagues to suggest that self-identified African Americans may be distinguished

from white people in the United States. Genetic similarities between African Americans and sub-Saharan Africans are identifiable, although the 2 populations are far from a perfect match (13). (Sub-Saharan Africans are one of the most genetically diverse populations on the globe [14].) On the basis of findings such as these, would it be inappropriate to assign an African-American patient to the "black race" category and to select treatment based on the minor genetic differences that Tang and colleagues used to distinguish these populations? Let us address this question in the context of cardiovascular disease.

African Americans have higher rates of hypertension than white people in the United States. (Sub-Saharan Africans have one of the lowest rates of hypertension in the world, substantially lower than that of U.S. and European white people [15].) In addition, African Americans with hypertension show less of a response than U.S. white people when treated with angiotensin-converting enzyme (ACE) inhibitors (16). One explanation may be the increased prevalence in certain black populations of a mutation in a gene that regulates the renin–angiotensin system in the kidney (17) and may be associated with an increased risk for hypertension (18). On the basis of the possibly higher prevalence of the mutation in the U.S. black population, should physicians avoid ACE inhibitors in their black patients?

A recent study looked specifically at the use of an ACE inhibitor to treat high blood pressure in black and white patients. In a simple bivariate comparison, the medication was less effective in black patients than in white patients. However, when the researchers then considered the individual characteristics of the patients, such as body size and pretreatment hypertension severity, most differences in effect went away. This led the researchers to conclude "that a large source of variability of blood pressure response to treatment is within, not between, racial groups, and that factors that vary at the level of the individual contribute to apparent racial differences in response to treatment" (19).

A recent meta-analysis, examining 15 published studies involving more than 10 000 patients, confirmed that ACE inhibitors, as well as β-blockers, have less of an antihypertensive effect in black patients than in white patients. However, the difference in effect was small (between 0.6 and 3.0 mm Hg) and only affected between 5% and 20% of the patients (depending on the study), leading the authors to conclude that "approximately 80% to 95% of whites and blacks *have similar responses to commonly used antihypertensive drugs*" [italics added] (20).

To state that, on average, the antihypertensive effect of β-blockers and ACE inhibitors is slightly smaller for black people than for white people is technically accurate. However, small differences across thousands of patients, despite meeting tests of statistical significance, say little about how a particular patient will respond. To use such differences to decide that *all* black patients should not get these drugs *would risk treating more than 9 out of 10 black patients inappropriately* by withholding drugs that are as likely to have a beneficial effect as in white patients.

Another problem in which severe racial disparities exist in the United States is congestive heart failure (CHF). African-American patients with CHF are much more likely to die of their disease than white patients (21). One study's explanation for this disparity is the increased presence of a mutation in African Americans that increases the likelihood of CHF (22). An editorial accompanying the study, however, wisely cautioned that the findings might represent "a spurious association between a polymorphism and a disease simply because both the disease and the [genetic mutation] are found in the same population" (23).

This issue—whether the presence of gene mutations within the black population explains differing patterns of disease between African-American and white patients—is crucial, especially in light of the common suggestion that we move toward race-based pharmaceutical therapy for treating CHF. Two studies of the treatment of CHF were published simultaneously, 1 study suggesting that ACE inhibitors were effective in white patients but not in black patients (24) and the other study suggesting that β-blockers were equally effective in both white and black patients (25). The authors of the first study concluded that "therapeutic recommendations may need to be tailored according to racial background" (24). An accompanying editorial supported this view, stating that "racial differences in response to drugs not only have practical importance for the choice and dose of drugs but should also alert physicians to important underlying genetic determinants of drug response" (26). Others took an opposing view, suggesting that such arguments "are based on nonsignificant findings or genetic variation that does not have an established association with the disease being studied" (27).

From the results of these 2 studies, practitioners may seem to act in the best interest of their patients if they use ACE inhibitors for white patients with CHF but not for black patients with CHF. As reasonable as this conclusion seems on the surface, to follow it may leave many black patients inadequately treated. This may be true for 2 reasons. First, the study suggesting a lack of effectiveness of ACE inhibitors in black patients relied on a single measure of effect (rate of hospitalization). An author of the study published a subsequent paper, using the same data set, that came to a different conclusion but received much less publicity. When the author and colleagues assessed the effect of ACE inhibitors in any of 3 different ways that measure the progression of CHF to either more severe symptoms or death, they found that the ACE inhibitor "was equally efficacious" in black and white patients (28).

Second, CHF may be due to different causes in different people. It can be caused either by ischemic damage to the heart muscle from atherosclerosis (ischemic CHF) or by a chronic strain on the heart due to complications that often result from hypertension, diabetes, and kidney disease (nonischemic CHF). White patients are substantially

more likely to have ischemic CHF, and black patients are much more likely to have nonischemic CHF (21, 22, 29). The combination of higher rates of hypertension, diabetes, and kidney disease in black patients with CHF explains much of the higher death rate of CHF in all black patients, both those receiving treatment and those in placebo control groups (24, 25, 28).

Chronic kidney disease is a predictor of death from cardiovascular disease in general (30) and CHF in particular (31). Angiotensin-converting enzyme inhibitors and their newer cousin angiotensin-II–receptor blockers are both effective in reducing cardiovascular disease in patients with diabetes and kidney disease (32). To systematically avoid ACE inhibitors in black patients with CHF on the belief that race accurately predicts genetic traits and therefore drug response will leave a substantial segment of those patients—especially those with chronic kidney disease—inadequately treated and without the proven benefit of these drugs.

In addition to deciding whether scientific studies warrant withholding certain medicines from black patients, practitioners must also decide whether certain medicines are effective for only black patients. The U.S. Food and Drug Administration (FDA) recently approved a fixed combination of isosorbide dinitrate and hydralazine (ISD-H) for use only in black patients with CHF. The Vasodilator Heart Failure Trial (V-HeFT) I and II trials originally studied this combination in the 1980s and found it may benefit patients with CHF (33, 34). A subsequent reanalysis of the data suggested that this benefit was more pronounced for black patients than for white patients (35). A follow-up, placebo-controlled trial involving only black patients (the African-American Heart Failure Trial [A-HeFT]) confirmed a beneficial effect of ISD-H in treating CHF when added to standard therapy (36).

Isosorbide dinitrate and hydralazine exerts its beneficial effect in patients with CHF by increasing the level of nitric oxide and decreasing oxidant stress in the vascular endothelium and thereby increasing vasodilation (37). In a report submitted to the FDA (38), the pharmaceutical company holding the patent on ISD-H suggested that the race-specific effect of ISD-H may be due to an increased prevalence of a rare genetic mutation among black people (39) that results in reduced nitric oxide levels in the endothelial cells (40). The FDA's medical reviewer could not confirm a genetic basis for the effect of ISD-H in black patients and identified many alternative explanations (41).

One alternative explanation for racial differences in vascular nitric oxide activity is the substantially higher rate of diabetes among black people (10.1%) compared with white people (6.1%) in the United States (42). Decreased endothelial levels of nitric oxide are a principal contributor to the vascular damage associated with diabetes (43–46). Glycated hemoglobin levels and tissue nitric oxide levels are inversely associated (47–49), suggesting that those with worse diabetic control are more susceptible to the adverse effects of nitric oxide deficit. The co-existence of diabetes and hypertension may magnify this effect (50, 51). We would thus expect to see a greater beneficial effect for ISD-H in patients with diabetes.

Table 2. **Rates of Diabetes in the Trials Testing the Effectiveness of Isosorbide Dinitrate–Hydralazine and in the Studies of Left Ventricular Dysfunction***

Trial, Year (Reference)	Patients with Diabetes, %
ISD-H trials	
V-HeFT I, 1986 (33)	17.2 (treatment); 24.5 (control)
V-HeFT II, 1991 (34)	20.0 (treatment); 20.8 (control)
A-HeFT, 2004 (36)†	44.8 (treatment); 37.0 (control)
SOLVD, 1999 (21)‡	28.5 (black); 17.4 (white)

* A-HeFT = African-American Heart Failure Trial; ISD-H = isosorbide dinitrate–hydralazine; SOLVD = Studies of Left Ventricular Dysfunction; V-HeFT = Vasodilator Heart Failure Trial.
† Differences in rates are significant ($P \leq 0.01$).
‡ Percentages are for combined prevention and treatment trials. Differences in rates are significant ($P \leq 0.01$).

Table 2 shows the rates of diabetes in the 3 trials on the effect of ISD-H in CHF. Diabetes rates in the V-HeFT trials were substantially lower than those in the A-HeFT trials. The V-HeFT trials did not report diabetes prevalence by race; however, another large study involving 5719 white patients and 800 black patients with left ventricular dysfunction (Studies of Left Ventricular Dysfunction [SOLVD] [21]) found that prevalence of diabetes among the black patients was 64% greater than that among white patients—the same difference in prevalence as in the general population. Thus, the prevalence of diabetes among patients in the treatment group of the A-HeFT study was statistically significantly greater than that among the patients in the control group and was substantially greater than that among all patients with CHF, black or white.

It is reasonable to expect ISD-H to be of benefit in a targeted population of patients with CHF and high rates of coexistent diabetes—such as that in the A-HeFT trial—regardless of the patients' race. Similarly, ISD-H may be less useful in patients—black or white—with isolated ischemic CHF who don't have the added impairment of endothelial nitric oxide associated with diabetes. To select patients to receive ISD-H on the basis of their "race" risks withholding a potentially useful medication from some nonblack patients, while using it inappropriately in some black patients.

Summary and Conclusions

In the words of Francis Collins, director of the National Human Genome Research Institute (52):

> "Race" and "ethnicity" are poorly defined terms that serve as flawed surrogates for multiple environmental and genetic factors in disease causation. . . . Research must move beyond these weak and imperfect proxy relationships to define the more proximate factors that influence health.

Variation within races and large ethnic groups is so broad that attempts to use race as a proxy risks the inappropriate withholding of treatment from a patient who has individual characteristics that are atypical of the average of the larger group. Instead, the disease risk of an individual patient is a "complex interplay between an unknown constellation of genetic variants, environmental factors, lifestyle characteristics and some stochastic processes" (53). Race does a poor job of capturing this complexity.

A practitioner will best serve a patient's needs by looking *beyond* race to acquire knowledge of that patient's *individual* socioeconomic, cultural, behavioral, and ancestral circumstances. Without specific knowledge of these individual circumstances, attempts to use race as a proxy is fraught with the danger of inappropriate treatment and may perpetuate rather than eliminate racial disparities in care.

From Stanford University, Stanford, California.

Potential Financial Conflicts of Interest: None disclosed.

Requests for Single Reprints: Donald A. Barr, MD, PhD, Department of Sociology, Stanford University, Building 120, MC 2047, Stanford, CA 94305-2047; e-mail, barr@stanford.edu.

References

1. **Leroi AM.** A family tree in every gene. New York Times. 14 March 2005:A21.
2. **Satel S.** I am a racially profiling doctor. New York Times Magazine. 5 May 2002:56.
3. **Schwartz RS.** Racial profiling in medical research [Editorial]. N Engl J Med. 2001;344:1392-3. [PMID: 11333999]
4. **Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, Zhivotovsky LA, et al.** Genetic structure of human populations. Science. 2002;298:2381-5. [PMID: 12493913]
5. Moor. In: Oxford English Dictionary. Accessed at www.oed.com on 28 March 2005.
6. **Grieco EM, Cassidy RC.** Overview of Race and Hispanic Origin. Census 2000 Brief. Washington, DC: U.S. Census Bureau; March 2001. Accessed at www.census.gov/prod/2001pubs/c2kbr01-1.pdf on 27 September 2005.
7. **Risch N, Burchard E, Ziv E, Tang H.** Categorization of humans in biomedical research: genes, race and disease. Genome Biol. 2002;3:comment2007. [PMID: 12184798]
8. **Phimister EG.** Medicine and the racial divide. N Engl J Med. 2003;348:1081-2. [PMID: 12646663]
9. **Rotimi CN.** Genetic ancestry tracing and the African identity: a double-edged sword? Developing World Bioeth. 2003;3:151-8. [PMID: 14768647]
10. **Zachary AA, Bias WB, Johnson A, Rose SM, Leffell MS.** Antigen, allele, and haplotype frequencies report of the ASHI minority antigens workshops: part 1, African-Americans. Hum Immunol. 2001;62:1127-36. [PMID: 11600220]
11. **Kittles RA, Chen W, Panguluri RK, Ahaghotu C, Jackson A, Adebamowo CA, et al.** CYP3A4-V and prostate cancer in African Americans: causal or confounding association because of population stratification? Hum Genet. 2002;110:553-60. [PMID: 12107441]
12. **Tang H, Quertermous T, Rodriguez B, Kardia SL, Zhu X, Brown A, et al.** Genetic structure, self-identified race/ethnicity, and confounding in case-control association studies. Am J Hum Genet. 2005;76:268-75. [PMID: 15625622]
13. **Parra EJ, Kittles RA, Shriver MD.** Implications of correlations between skin color and genetic ancestry for biomedical research. Nat Genet. 2004;36:S54-60. [PMID: 15508005]
14. **Cao K, Moormann AM, Lyke KE, Masaberg C, Sumba OP, Doumbo OK, et al.** Differentiation between African populations is evidenced by the diversity of alleles and haplotypes of HLA class I loci. Tissue Antigens. 2004;63:293-325. [PMID: 15009803]
15. **Cooper RS, Wolf-Maier K, Luke A, Adeyemo A, Banegas JR, Forrester T, et al.** An international comparative study of blood pressure in populations of European vs. African descent. BMC Med. 2005;3:2. [PMID: 15629061]
16. **Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al.** The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560-72. [PMID: 12748199]
17. **Jorde LB, Wooding SP.** Genetic variation, classification and 'race'. Nat Genet. 2004;36:S28-33. [PMID: 15508000]
18. **Kunz R, Kreutz R, Beige J, Distler A, Sharma AM.** Association between the angiotensinogen 235T-variant and essential hypertension in whites: a systematic review and methodological appraisal. Hypertension. 1997;30:1331-7. [PMID: 9403549]
19. **Mokwe E, Ohmit SE, Nasser SA, Shafi T, Saunders E, Crook E, et al.** Determinants of blood pressure response to quinapril in black and white hypertensive patients: the Quinapril Titration Interval Management Evaluation trial. Hypertension. 2004;43:1202-7. [PMID: 15117912]
20. **Sehgal AR.** Overlap between whites and blacks in response to antihypertensive drugs. Hypertension. 2004;43:566-72. [PMID: 14757779]
21. **Dries DL, Exner DV, Gersh BJ, Cooper HA, Carson PE, Domanski MJ.** Racial differences in the outcome of left ventricular dysfunction. N Engl J Med. 1999;340:609-16. [PMID: 10029645]
22. **Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB.** Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med. 2002;347:1135-42. [PMID: 12374873]
23. **Hajjar RJ, MacRae CA.** Adrenergic-receptor polymorphisms and heart failure [Editorial]. N Engl J Med. 2002;347:1196-9. [PMID: 12374881]
24. **Exner DV, Dries DL, Domanski MJ, Cohn JN.** Lesser response to angiotensin-converting-enzyme inhibitor therapy in black as compared with white patients with left ventricular dysfunction. N Engl J Med. 2001;344:1351-7. [PMID: 11333991]
25. **Yancy CW, Fowler MB, Colucci WS, Gilbert EM, Bristow MR, Cohn JN, et al.** Race and the response to adrenergic blockade with carvedilol in patients with chronic heart failure. N Engl J Med. 2001;344:1358-65. [PMID: 11333992]
26. **Wood AJ.** Racial differences in the response to drugs—pointers to genetic differences [Editorial]. N Engl J Med. 2001;344:1394-6. [PMID: 11336055]
27. **Cooper RS, Kaufman JS, Ward R.** Race and genomics. N Engl J Med. 2003;348:1166-70. [PMID: 12646675]
28. **Dries DL, Strong MH, Cooper RS, Drazner MH.** Efficacy of angiotensin-converting enzyme inhibition in reducing progression from asymptomatic left ventricular dysfunction to symptomatic heart failure in black and white patients. J Am Coll Cardiol. 2002;40:311-7. [PMID: 12106937]
29. **Moran AE, Cooper RS.** Isosorbide dinitrate and hydralazine in blacks with heart failure [Letter]. N Engl J Med. 2005;352:1041-3; author reply 1041-3. [PMID: 15758018]
30. **Hostetter TH.** Chronic kidney disease predicts cardiovascular disease [Editorial]. N Engl J Med. 2004;351:1344-6. [PMID: 15385664]
31. **Fonarow GC, Adams KF Jr, Abraham WT, Yancy CW, Boscardin WJ.** Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA. 2005;293:572-80. [PMID: 15687312]
32. **Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, et al.** Angiotensin-receptor blockade versus converting-enzyme inhibition in type 2 diabetes and nephropathy. N Engl J Med. 2004;351:1952-61. [PMID: 15516696]
33. **Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, et al.** Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314:1547-52. [PMID: 3520315]
34. **Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, et al.** A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med. 1991;325:303-10. [PMID: 2057035]
35. **Carson P, Ziesche S, Johnson G, Cohn JN.** Racial differences in response to therapy for heart failure: analysis of the vasodilator-heart failure trials. Vasodilator-Heart Failure Trial Study Group. J Card Fail. 1999;5:178-87. [PMID: 10496190]
36. **Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R Jr, Ferdinand K, et al.** Combination of isosorbide dinitrate and hydralazine in blacks with heart

failure. N Engl J Med. 2004;351:2049-57. [PMID: 15533851]
37. **Hare JM.** Nitroso-redox balance in the cardiovascular system [Editorial]. N Engl J Med. 2004;351:2112-4. [PMID: 15533853]
38. BiDil (Isosorbide Dinitrate and Hydralazine Hydrochloride) Tablets. NDA 20-727. FDA Advisory Committee Briefing Document. Lexington, MA: NitroMed, Inc.; 16 June 2005. Accessed at www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4145B2_02_01-NitroMed-Background.htm on 8 August 2005.
39. **Li R, Lyn D, Lapu-Bula R, Oduwole A, Igho-Pemu P, Lankford B, et al.** Relation of endothelial nitric oxide synthase gene to plasma nitric oxide level, endothelial function, and blood pressure in African Americans. Am J Hypertens. 2004;17:560-7. [PMID: 15233974]
40. **Kalinowski L, Dobrucki IT, Malinski T.** Race-specific differences in endothelial function: predisposition of African Americans to vascular diseases. Circulation. 2004;109:2511-7. [PMID: 15159296]
41. **Lemtouni S.** Clinical Review - Submission Number 20-727, Hydralazine HCl and Isosorbide dinitrate. 12/23/04. Accessed at www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4145b2_Table%20of%20Contents.htm on 8 August 2005.
42. **Lethbridge-Cejku M, Schiller JS, Bernadel L.** Summary health statistics for U.S. adults: National Health Interview Survey, 2002. Vital Health Stat 10. 2004;(222):1-151. [PMID: 15791763]
43. **Gunnett CA, Heistad DD, Faraci FM.** Gene-targeted mice reveal a critical role for inducible nitric oxide synthase in vascular dysfunction during diabetes. Stroke. 2003;34:2970-4. [PMID: 14657549]
44. **Endemann DH, Schiffrin EL.** Nitric oxide, oxidative excess, and vascular complications of diabetes mellitus. Curr Hypertens Rep. 2004;6:85-9. [PMID: 15010009]
45. **Triggle CR, Ding H, Anderson TJ, Pannirselvam M.** The endothelium in health and disease: a discussion of the contribution of non-nitric oxide endothelium-derived vasoactive mediators to vascular homeostasis in normal vessels and in type II diabetes. Mol Cell Biochem. 2004;263:21-7. [PMID: 15524164]
46. **Woodman RJ, Playford DA, Watts GF.** Basal production of nitric oxide (NO) and non-NO vasodilators in the forearm microcirculation in Type 2 diabetes: Associations with blood pressure and HDL cholesterol. Diabetes Res Clin Pract. 2005. [PMID: 16029909]
47. **James PE, Lang D, Tufnell-Barret T, Milsom AB, Frenneaux MP.** Vasorelaxation by red blood cells and impairment in diabetes: reduced nitric oxide and oxygen delivery by glycated hemoglobin. Circ Res. 2004;94:976-83. [PMID: 14963010]
48. **Xiong Y, Lei M, Fu S, Fu Y.** Effect of diabetic duration on serum concentrations of endogenous inhibitor of nitric oxide synthase in patients and rats with diabetes. Life Sci. 2005;77:149-59. [PMID: 15862600]
49. **Xu B, Ji Y, Yao K, Cao YX, Ferro A.** Inhibition of human endothelial cell nitric oxide synthesis by advanced glycation endproducts but not glucose: relevance to diabetes. Clin Sci (Lond). 2005. [PMID: 16022682]
50. **Brands MW, Bell TD, Gibson B.** Nitric oxide may prevent hypertension early in diabetes by counteracting renal actions of superoxide. Hypertension. 2004;43:57-63. [PMID: 14656952]
51. **Dixon LJ, Hughes SM, Rooney K, Madden A, Devine A, Leahey W, et al.** Increased superoxide production in hypertensive patients with diabetes mellitus: role of nitric oxide synthase. Am J Hypertens. 2005;18:839-43. [PMID: 15925745]
52. **Collins FS.** What we do and don't know about 'race', 'ethnicity', genetics and health at the dawn of the genome era. Nat Genet. 2004;36:S13-5. [PMID: 15507997]
53. **Rotimi CN.** Are medical and nonmedical uses of large-scale genomic markers conflating genetics and 'race'? Nat Genet. 2004;36:S43-7. [PMID: 15508002]